nature REVIEWS

ENDOCRINOLOGY

Type 2 diabetes mellitus

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Over the past three decades, the number of people with T2DM has more than doubled globally, making this disease one of the most important public health challenges of the 21st century. The causes of the T2DM epidemic are embedded in a complex group of genetic and epigenetic determinants interacting within an equally complex societal framework that incorporates behavioural and environmental influences. Increasing numbers of children and adolescents are now being clinically diagnosed with T2DM, and, in some countries such as Japan and in indigenous communities in Australia, Canada and New Zealand, T2DM is becoming more prevalent than type 1 diabetes mellitus. The prevention and treatment of T2DM and the control of its microvascular and macrovascular complications will require not only pharmacological approaches but also a major integrated approach directed at societal and individual behavioural change. Only then may there be a marked reduction in the high levels of premature morbidity and mortality caused by this disease.

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Risk factors for T2DM

In the past few decades, research into risk factors for T2DM has focused on genetic susceptibility to β-cell dysfunction. Major roles have been identified for several genes, although their contribution to an individual's risk of T2DM is influenced by environmental and behavioural factors, including a sedentary lifestyle, increased nutrient intake and obesity. The contribution of the maternal environment and *in utero* factors to the risk of T2DM in subsequent generations, via epigenetic modification, is now being highlighted as potentially important in explaining the high rates of T2DM currently seen in many populations in the developing world. It is these communities that are bearing the brunt of the epidemic.
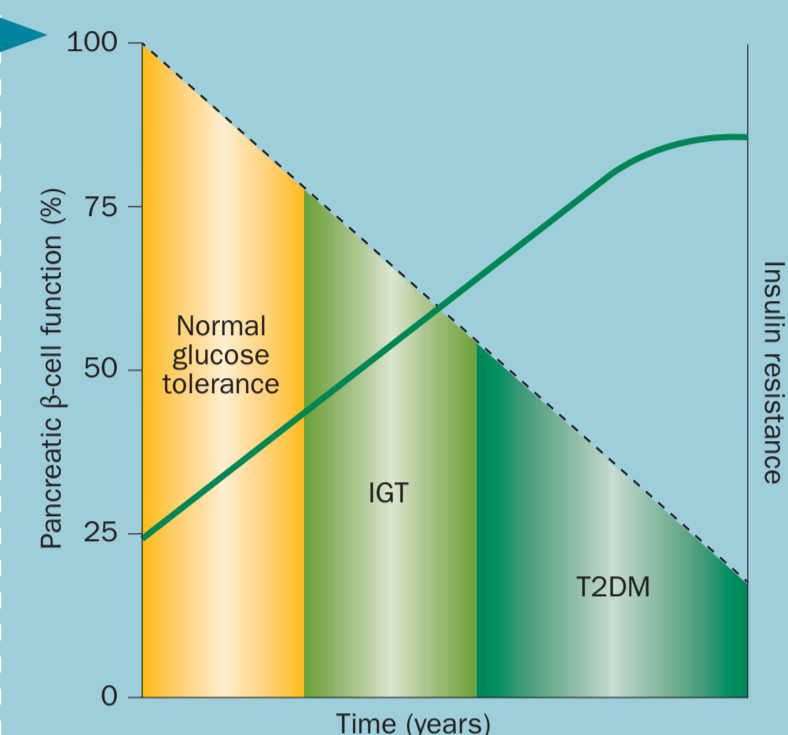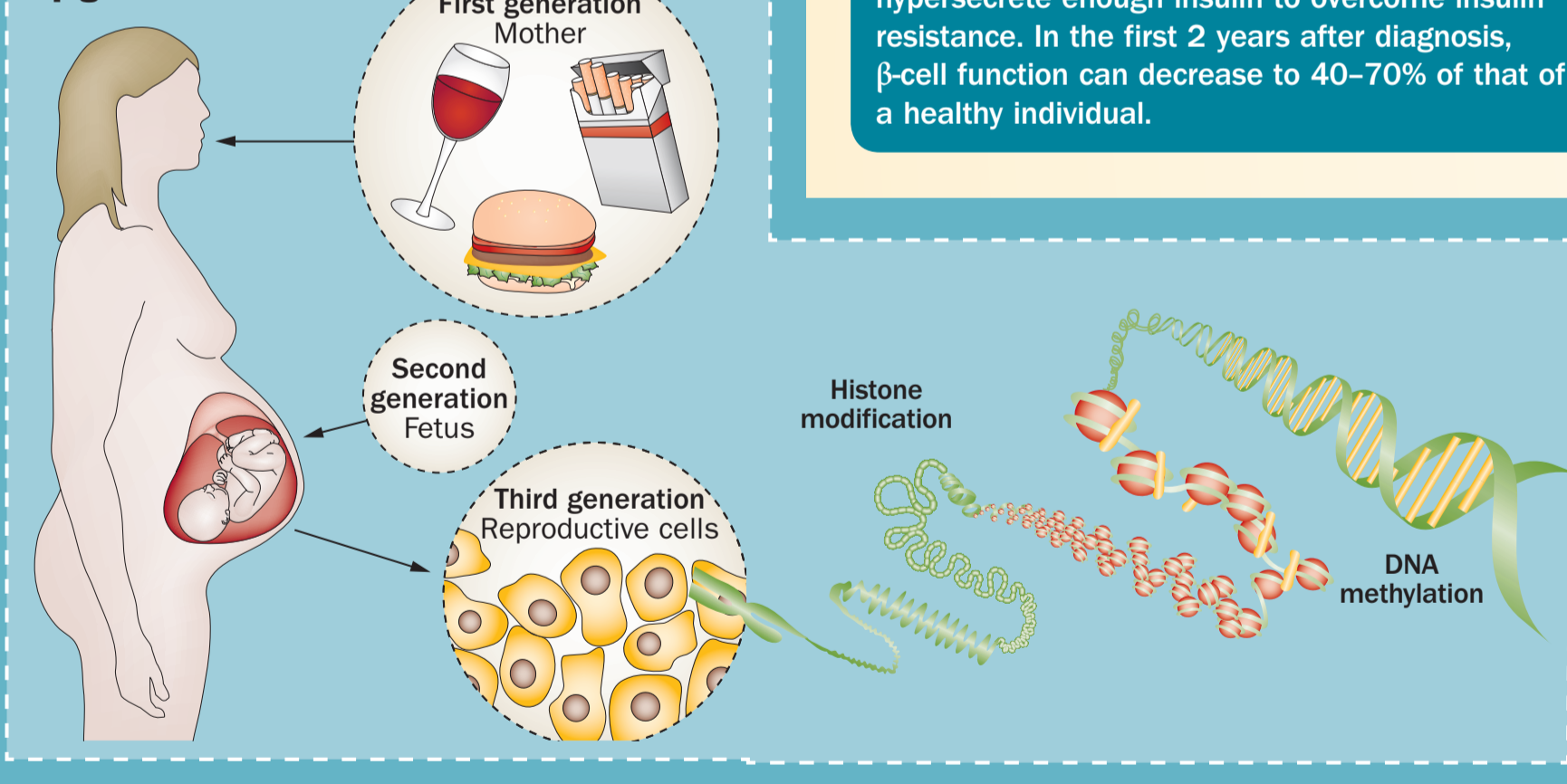
Genetic factors

Genes implicated in:
- β-cell dysfunction e.g. *GCK, HNF1A, HNF4A, TCF7L2*
- Insulin resistance e.g. *FTO, IRS1, PPARG*

Environmental factors

Early life
- Intrauterine factors
- Low birth weight
- Poor nutrition

Adult life
- Obesity
- Sedentary behaviour
- Nutrient excess

Epigenetic factors

First generation — Mother
Second generation — Fetus
Third generation — Reproductive cells
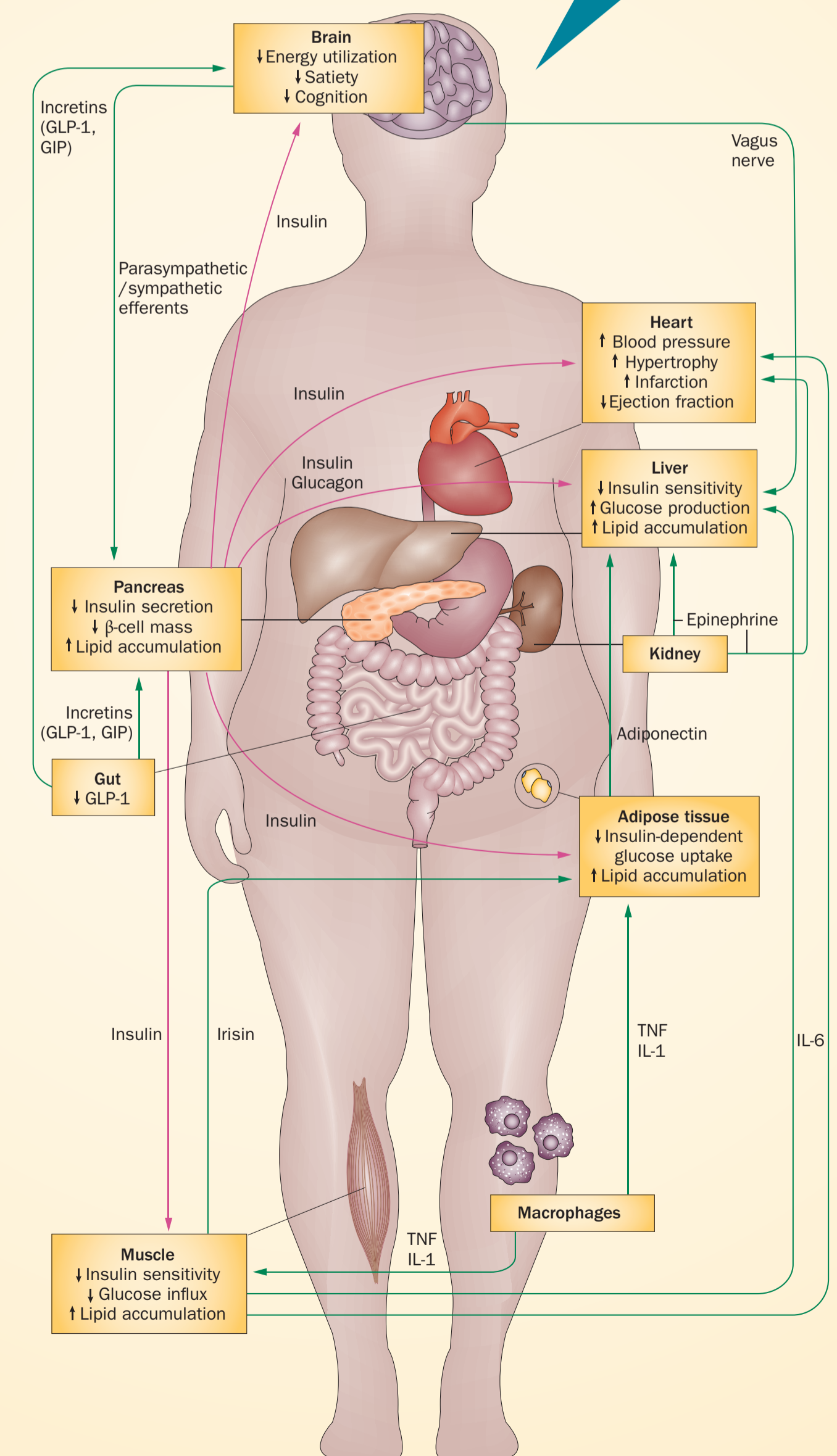
Histone modification

DNA methylation

Clinical stages of T2DM

Epidemiological studies suggest that the onset of T2DM can occur 5–10 years before clinical diagnosis. In the preclinical phase, when β-cell function is not impaired, the ability of β cells to hypersecrete insulin masks the presence of IGT, often for several years. During this phase, fasting plasma glucose concentrations are above the upper limit of the normal range, but below the threshold diagnostic of T2DM (110–126 mg/dl or 6.1–7.0 mmol/l). As β-cell function starts to decline, mild postprandial hyperglycaemia develops, reflecting the inability of β cells to hypersecrete enough insulin to overcome insulin resistance. In the first 2 years after diagnosis, β-cell function can decrease to 40–70% of that of a healthy individual.

Pancreatic β-cell function (%): Normal glucose tolerance / IGT / T2DM

Insulin resistance

Time (years)

Epidemiology and prevalence of T2DM

According to the IDF, 366 million people currently have diabetes worldwide and over 90% of them have T2DM. When compared with other regions, the Western Pacific region currently has the most people with diabetes (132 million people). Most of these people have T2DM. However, the countries with the largest numbers of people with T2DM are China, India, USA, Brazil and the Russian Federation. By 2030, the IDF predicts that the total number of people with diabetes will have risen to 552 million, of whom over half will remain undiagnosed. The greatest increases in prevalence are predicted to occur in Africa and the Middle East.
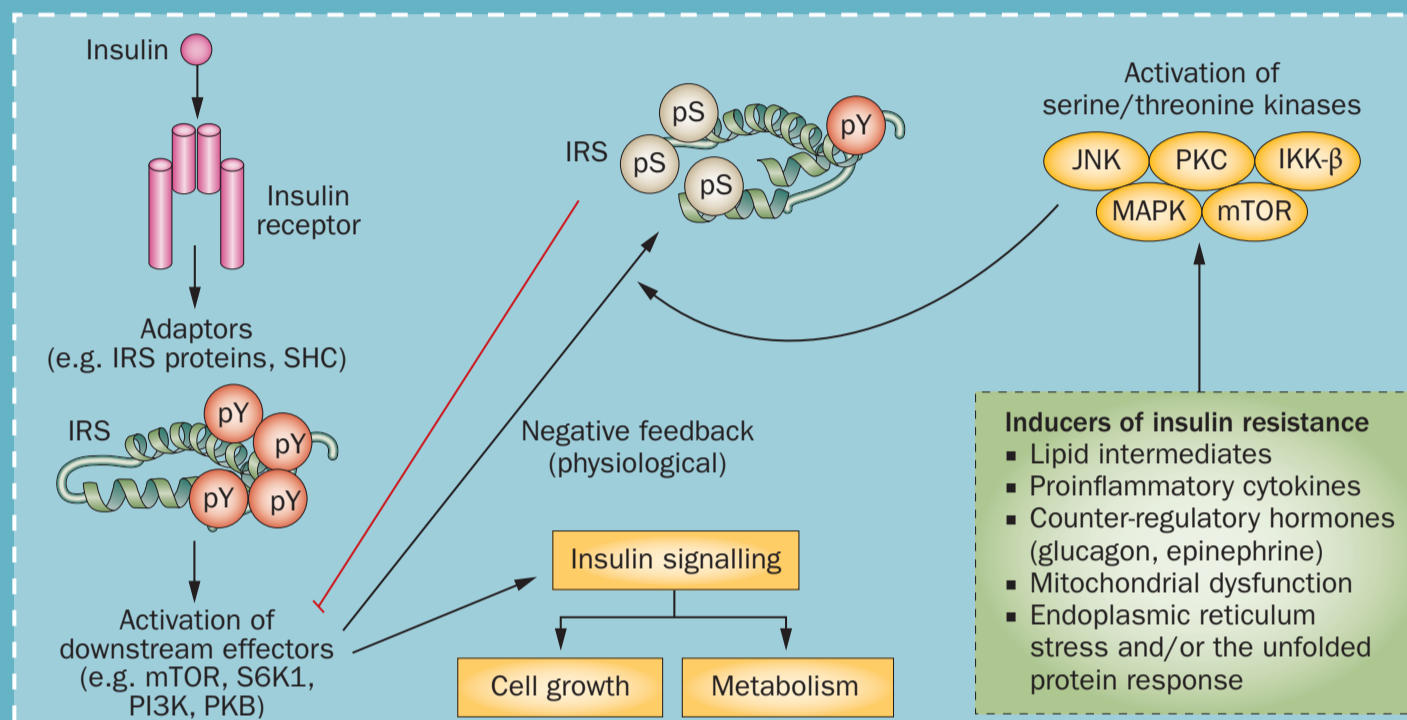
Contribution of key organs

Various organs seem to have crucial roles in the multifactorial pathogenesis of T2DM. The endocrine cells of the pancreas include β cells, which secrete insulin, and α cells, which secrete glucagon. The brain is involved in regulation of appetite and satiety, as well as in modulating pancreatic α-cell and β-cell function. The liver is a major source of glucose production through glycogenolysis. Skeletal muscle (and, to a lesser extent, adipose tissue) is a major site of glucose uptake in response to insulin. Indeed, an increase in visceral adipose tissue deposition, leading to central obesity and increased production of proinflammatory adipokines, is strongly associated with an elevated risk of T2DM and cardiovascular disease. Increasingly, certain hormones and cytokines have been identified as pivotal in modulating communication among the various organs of the body and thereby controlling glucose homeostasis. All of these metabolic pathways are implicated in the pathogenesis of T2DM.
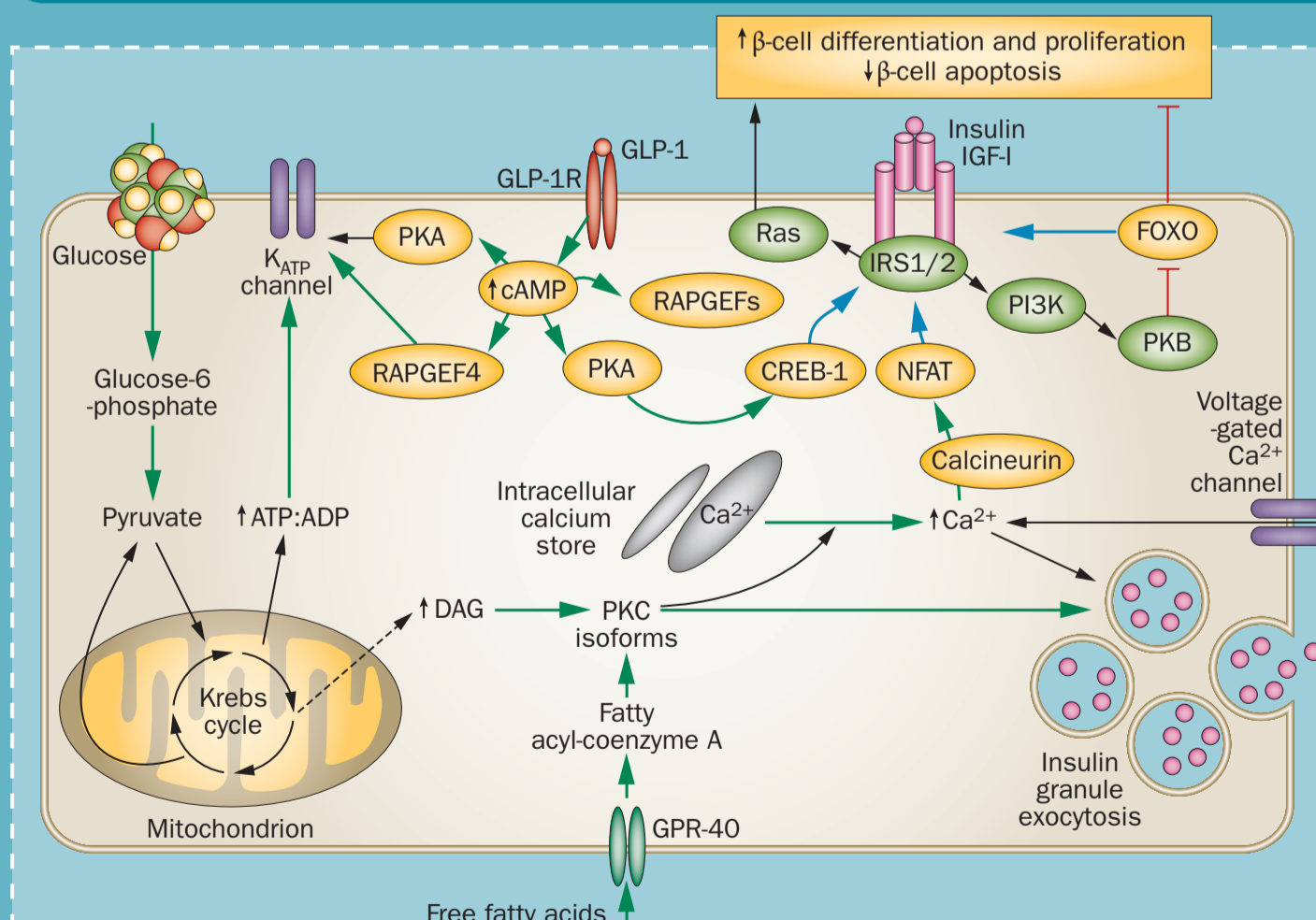
Brain — ↓ Energy utilization, ↓ Satiety, ↓ Cognition

Incretins (GLP-1, GIP)

Insulin

Vagus nerve

Parasympathetic/sympathetic efferents

Heart — ↑ Blood pressure, ↑ Hypertrophy, ↑ Infarction, ↓ Ejection fraction

Liver — ↓ Insulin sensitivity, ↑ Glucose production, ↑ Lipid accumulation

Insulin Glucagon

Pancreas — ↓ Insulin secretion, ↓ β-cell mass, ↑ Lipid accumulation

Epinephrine

Kidney

Incretins (GLP-1, GIP)

Gut — ↓ GLP-1

Adiponectin

Insulin

Adipose tissue — ↓ Insulin-dependent glucose uptake, ↑ Lipid accumulation

TNF, IL-1

IL-6

Insulin

Irisin

Muscle — ↓ Insulin sensitivity, ↓ Glucose influx, ↑ Lipid accumulation

TNF, IL-1

Macrophages

Mechanisms of T2DM

T2DM is a heterogeneous condition resulting from β-cell dysfunction and insulin resistance, either one of which may predominate in a given individual, as a result of the interaction of genetic and environmental risk factors. Many pathways can promote both insulin resistance and β-cell dysfunction, including oxidative stress, endoplasmic reticulum stress and inflammation.

Insulin

Insulin receptor

Adaptors (e.g. IRS proteins, SHC)

IRS — pY

IRS — pS / pY

Activation of serine/threonine kinases — JNK, PKC, IKK-β, MAPK, mTOR

Negative feedback (physiological)

Activation of downstream effectors (e.g. mTOR, S6K1, PI3K, PKB)

Insulin signalling — Cell growth / Metabolism

Inducers of insulin resistance
- Lipid intermediates
- Proinflammatory cytokines
- Counter-regulatory hormones (glucagon, epinephrine)
- Mitochondrial dysfunction
- Endoplasmic reticulum stress and/or the unfolded protein response

Insulin resistance

Insulin resistance—a state in which the capacity of target cells to respond to normal insulin levels is reduced—has a central role in the development of T2DM. Inducers of insulin resistance act, at least in part, by activating various serine/threonine kinases that phosphorylate IRS proteins as well as other components of the insulin signalling pathway. In so doing, they exploit negative feedback control mechanisms otherwise utilized by insulin itself to terminate insulin signal transduction. Phosphorylation of IRS proteins inhibits their function and interferes with insulin signalling in a number of ways, leading to the development of an insulin-resistant state.

↑β-cell differentiation and proliferation
↓β-cell apoptosis

Insulin IGF-I

Glucose

K_{ATP} channel

Glucose-6-phosphate

Pyruvate

↑ATP:ADP

PKA, cAMP, RAPGEF4, RAPGEFs, PKA, CREB-1, NFAT, Ras, IRS1/2, PI3K, PKB, FOXO

GLP-1R / GLP-1

Calcineurin

Voltage-gated Ca^{2+} channel

Intracellular calcium store

Ca^{2+} ↑Ca^{2+}

Krebs cycle

Mitochondrion

↑DAG

PKC isoforms

Fatty acyl-coenzyme A

GPR-40

Free fatty acids

Insulin granule exocytosis

β-cell dysfunction

Glucose is transported into pancreatic β cells by facilitated diffusion. Oxidative metabolism of glucose leads to an increase in intracellular ATP and closure of K_{ATP} channels, leading to membrane depolarization and an influx of Ca^{2+} that triggers exocytosis of insulin. High levels of intracellular glucose in pancreatic β cells also stimulates Ca^{2+}-independent pathways that further increase insulin secretion. These pathways involve enhanced glucokinase activity, increases in citrate levels, increased DAG formation and enhanced PKC signalling. Incretins (such as GLP-1) are increasingly being explored for therapeutic purposes. Binding of GLP-1 to its receptor promotes insulin release via intermediates such as PKB, and also increases β-cell mass via improved cell survival and decreased apoptosis.

Abbreviations

CREB-1	cAMP responsive element-binding protein
DAG	diacylglycerol
FOXO	forkhead box protein O
FTO	fat mass and obesity associated
GCK	glucokinase (hexokinase 4)
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide 1
GLP-1R	glucagon-like peptide 1 receptor
GPR-40	free fatty acid receptor 1
HNF1A	HNF1 homeobox B
HNF4A	hepatocyte nuclear factor 4 α
IDF	International Diabetes Federation
IGF-I	insulin-like growth factor I
IGT	impaired glucose tolerance
IKK-β	inhibitor of nuclear factor κB kinase subunit β
IRS	insulin receptor substrate
JNK	stress-activated protein kinase
MAPK	mitogen activated protein kinase
mTOR	serine/threonine protein kinase mTOR
NFAT	nuclear factor of activated T-cells
PI3K	phosphatidylinositol 3-kinase
PKA	protein kinase A
PKB	RAC-α serine/threonin protein kinase
PKC	protein kinase C
PPARG	peroxisome proliferator-activated receptor γ
pS	phosphoserine
pY	phosphotyrosine
RAPGEF	RAP guanine nucleotide exchange factor
SHC	SHC-transforming protein 1
S6K1	p70 S6 kinase
T2DM	type 2 diabetes mellitus
TCF7L2	transcription factor 7-like 2 (T-cell-specific, HMG box)
TNF	tumour necrosis factor

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